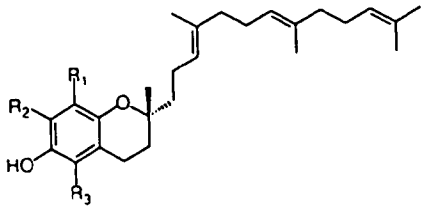
EXHIBT 1

Chart I

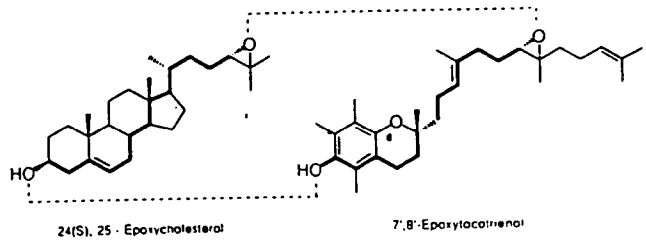


compound	R_1	R_2	R_3	ref
α-tocotrienol	Me	Me	Me	11a,b,e
β-tocotrienol	Me	H	Me	11a,e
γ-tocotrienol	Me	Me	H	11c,e
δ-tocotrienol	Me	H	H	11c,f
tocotrienol	H	H	H	11d

CoA reductase (HMGR) as measured by hepatic HMGR activity.[7] HMG-CoA reductase converts HMG-CoA into mevalonate and is the rate limiting enzyme in the cholesterol biosynthetic pathway.[13] Inhibition or suppression at the level of HMGR represents an attractive point of intervention since only early stage (water-soluble) products are accumulated. HMG-CoA reductase mass (activity) is diminished by tocotrienols through decreased synthesis and enhanced degradation of the reductase[12] and should be distinguished from competitive inhibitors such as mevinolin. The possibility to exploit a natural feedback mechanism of cholesterol regulation was apparent.[14]

In several repects, the tocotrienols appear to operate in a similar manner to oxysterols. Certain oxysterols have been shown to regulate cholesterol biosynthesis by a transcriptional down-regulation of the reductase gene.[15] It has been postulated that endogenously produced oxysterols are natural regulators of cholesterol biosynthesis. In particular, 24(*S*),25-epoxycholesterol and 25-hydroxycholesterol have been found in human liver, in vivo, in concentrations high enough for cholesterol regulation.[16] These oxysterols are potent repressors of HMG-CoA reductase and bind strongly to the cytosolic oxysterol binding protein.[17]

Early on it was apparent, that if oxysterols are indeed natural regulators of cholesterol biosynthesis, then the tocotrienols may have a similar function, since they appeared to cause the same effect (suppression of HMGR). In fact, Dreiding models[18] indicate that 24,25-epoxycholesterol and a 7′,8′-epoxy-α-tocotrienol share close structural resemblance. This relationship was confirmed by energy-minimized comparisons using MM2 calculations.[19]



Thus, α-tocotrienol or an oxygenated analogue might behave as an oxysterol surrogate. This comparison suggests that the terminal prenyl unit in tocotrienol may not be necessary for expression of biological activity.

Tocotrienol Synthetic Program

The initial objective was to extend the original findings of Qureshi et al.[7] by examining chromatographic fractions of tocotrienol-rich extracts in a cholesterol biosynthesis assay in primary rat hepatocytes. From high protein barley flour[20] extracts were obtained which were purified by silica gel chromatography. It was confirmed that one band (of multiple components) did exhibit the anticipated cholesterol suppressive activity in the rat hepatocyte.

A synthetic program was initiated to prepare *d,l*-α-tocotrienol and analogues based on the oxysterol hypothesis. The synthetic lot of α-tocotrienol was considerably less active (in the rat hepatocyte) than anticipated based on the activity of the barley extract (even taking into account the fact that it is a racemic mixture). A palm oil extract was received, which is a tocotrienol-rich fraction

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(20) Miller Brewing Co., P.O. Box 482, Milwaukee, WI 53201.

Table VI. Effects of α-Tocopherol and α-, γ-, and δ-Tocotrienols on Lipid Metabolism in 6-Week-Old Male Chickens[a]

test compound	concentration in the diet, ppm	total cholesterol	LDL cholesterol	HDL cholesterol	HMGR activity
control		197 ± 5	76 ± 5	107 ± 7	1086 ± 114
d-α-tocopherol	20	190 ± 7	72 ± 6	113 ± 8	1296 ± 61
d-α-tocotrienol	20	155 ± 3	55 ± 6	102 ± 7	670 ± 31
d-γ-tocotrienol	20	151 ± 4	41 ± 8	102 ± 5	494 ± 23
d-δ-tocotrienol	20	141 ± 3	41 ± 7	99 ± 8	550 ± 34

[a] Data expressed as means ± SD; n = 10 chickens per group; cholesterol values expressed as mg/100 mL; HMGR activity expressed as picomoles of mevalonic acid synthesized per minute per mg of microsomal protein.

Table VII. Effects of Natural and Synthetic γ-Tocotrienols on Lipid Parameters in Chickens[a]

	d-γ-tocotrienol				*d,l*-γ-tocotrienol			
dose, ppm	total cholesterol	LDL cholesterol	HDL cholesterol	HMGR activity	total cholesterol	LDL cholesterol	HDL cholesterol	HMGR activity
control	180 ± 2	72 ± 1	104 ± 3	658 ± 15	180 ± 2	72 ± 1	104 ± 3	658 ± 15
15	141 ± 2	42 ± 2	97 ± 1	606 ± 5	143 ± 1	44 ± 1	97 ± 2	603 ± 9
30	132 ± 2	35 ± 1	95 ± 2	561 ± 10	138 ± 1	39 ± 1	97 ± 2	561 ± 7
45	125 ± 2	29 ± 1	94 ± 1	546 ± 12	132 ± 1	32 ± 2	96 ± 2	551 ± 16

[a] Data expressed as means ± SD; n = 6 chickens per group; cholesterol values expressed as mg/100 mL; HMGR values expressed as picomoles of mevalonic acid synthesized per minute per mg of microsomal protein.

ferent and that tocotrienols lacking the 5-methyl substituent present in α-tocotrienol possess significantly greater cholesterol synthesis suppressive activity. Furthermore, the racemic synthetic tocotrienols exhibit comparable biological activity to the natural tocotrienols in the cholesterol suppression assays (Tables V, VII). The triprenylated (farnesyl) analogues are more active in vitro than the diprenylated (geranyl)-containing compounds tested.

The data presented are consistent with the concept that a specific interaction of tocotrienols with a component of the regulatory mechanism controlling HMGR protein levels occurs in vitro in cells and in vivo.

The structure–activity relationships in the compounds studied suggest that γ- and δ-tocotrienols are optimal structures for this interaction. The hypocholesterolemic action and associated structure–activity relationship data of an expanded series of farnesylated benzopyrans is the subject of a forthcoming publication. Further mechanistic studies will reveal the nature of the macromolecular interactions coupling tocotrienols to HMGR expression.

Experimental Section

Melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 1800 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AM 300 spectrometer or a Varian Gemini 300 NMR spectrometer; nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (δ) expressed in parts per million (ppm) with tetramethylsilane as an internal standard. Mass spectra were measured on a Finnegan 4500 spectrometer (low resolution) or a kratos MS50 spectrometer (high resolution).

Thin-layer chromatography was performed on silica gel 60 F-254 plates purchased from E. Merck and Co. (visualization with iodine or phosphomolybdic acid); flash chromatography[43] was performed on fine silica (EM Sciences, 230–400 mesh). HPLC analyses were performed on a Spectra-Physics apparatus. All reactions were run under dry nitrogen unless otherwise indicated. Dry solvents were purchased from Aldrich, Milwaukee, WI in sure/seal bottles and transferred by syringe under nitrogen. Most commercially available starting materials did not require further purification.

Purification of Tocotrienol-Rich Fraction (TRF) from Palm Oil. Palm oil TRF was fractionated by flash chromatography, and the compounds were isolated without delay by solvent evaporation under vacuum and stored under nitrogen at −20 °C. A 1.059-g sample of palm oil was chromatographed on a 60 × 90 mm column of 230–400 mesh silica gel (gradient 40:1 to 30:1 hexanes–ether) taking 50-mL aliquots. Nine major fractions were recovered. Fractions 1 (160 mg), 3 (153 mg), 6 (158 mg), and 8 (76 mg) were one spot by TLC and were evaluated by 300-MHz PMR, IR, MS, and HPLC analysis.

Fractions 1, 3, 6, and 8 were shown to be >90% pure by PMR and HPLC and were identified as *d*-α-tocopherol, *d*-α-tocotrienol, *d*-γ-tocotrienol and *d*-δ-tocotrienol, respectively. Identification of these components was made from literature comparison of physical and spectroscopic data.[11]

HPLC analysis of the TRF revealed its composition to be *d*-α-tocopherol (26%), *d*-α-tocotrienol (18%), *d*-γ-tocotrienol (27%), and *d*-δ-tocotrienol (7%) by integration methods. The chromatographic separation of these components is possible, but is very tedious requiring large quantities of solvents and is limited to small amounts of palm oil. Treatment of the palm oil extract (23.2 g) with approximately 0.75 equiv of *tert*-butyldimethylsilyl chloride (based on MW ≃ 424, 6.18 g) and imidazole (3.7 g) in dimethylformamide (30 mL) for 18 h at 60 °C, preferentially silylates the δ-T3 followed by the γ-T3. Only traces of the α-T and α-T3 derivatize. After an ether extraction from water, the γ- and δ-T3 were isolated by flash chromatography (1:200 ether–hexanes) as a colorless oil (12 g). The free phenols are then regenerated in quantitative yield by treatment of the silyl ethers with tetra-*n*-butylammonium fluoride (23 mL, 1.0 M). The crude phenols were purified by flash chromatography (gradient 45:1 to 30:1 hexanes–ether) to yield 5.4 g of pure *d*-γ-T3 and 2.0 g of pure *d*-δ-T3.

***d*-α-Tocotrienol.** Light brown oil: IR (film) 3480, 2930, 1453, 1380, 1260, 1085 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3 H), 1.58 (s, 3 H), 1.60 (s, 6 H), 1.69 (s, 3 H), 1.81 (m, 2 H), 1.95–2.10 (m, 12 H), 2.12 (s, 6 H), 2.17 (s, 3 H), 2.63 (t, J = 6.9 Hz, 2 H), 4.18 (s, 1 H), 5.09–5.14 (m, 3 H); MS *m/e* 424 (M^+); $[\alpha]^{20}_D$ −2.9° (c = 1.0, $CHCl_3$).

***d*-γ-Tocotrienol.** Yellow oil: IR (film) 3420, 2930, 1450, 1430, 1225, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.60 (s, 3 H), 1.61 (s, 6 H), 1.69 (s, 3 H), 1.79 (m, 2 H), 1.95–2.10 (m, 12 H), 2.13 (s, 3 H), 2.14 (s, 3 H), 2.69 (t, J = 6.4 Hz, 2 H), 4.19 (s, 1 H), 5.08–5.14 (m, 3 H), 6.38 (s, 1 H); MS *m/e* 410 (M^+); $[\alpha]^{20}_D$ −5.2° (c = 1.0, $CHCl_3$).

***d*-δ-Tocotrienol.** Pale yellow oil: IR (film) 3370, 2920, 1473, 1375, 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.61 (s, 9 H), 1.69 (s, 3 H), 1.75 (m, 2 H), 1.95–2.10 (m, 12 H), 2.14 (s, 3 H), 2.71 (t, J = 6.8 Hz, 2 H), 4.17 (s, 1 H), 5.08–5.17 (m, 3 H), 6.39 (d, J = 2.8 Hz, 1 H), 6.49 (d, J = 2.9 Hz, 1 H); MS *m/e* 396 (M^+); $[\alpha]^{20}_D$ −2.2° (c = 1.0, $CHCl_3$).

3,4-Dihydro-6-[(2-methoxyethoxy)methoxy]-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-propanal (1). A mixture (about 60:40)[30] of 2,5,7,8-tetramethyl-2-(4-methyl-3-pentenyl)-2*H*-1-benzopyran-6-ol and its cyclized isomer (42.5 g, 0.15 mol) dissolved

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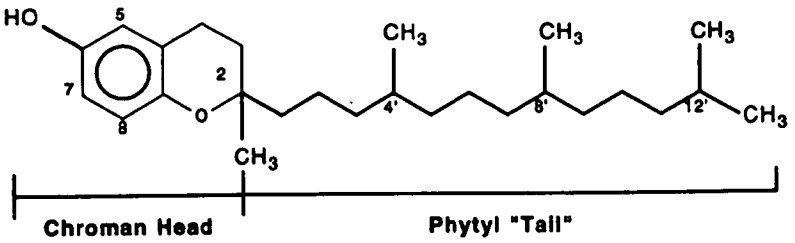
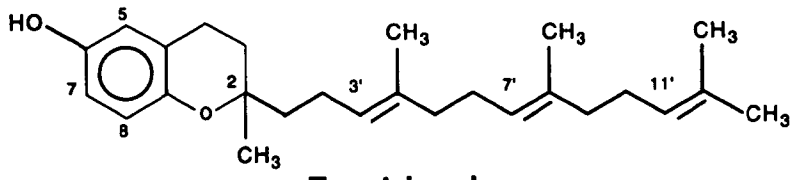
A



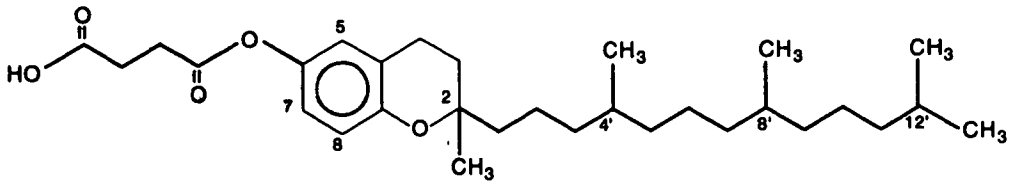
Tocopherols



Tocotrienols

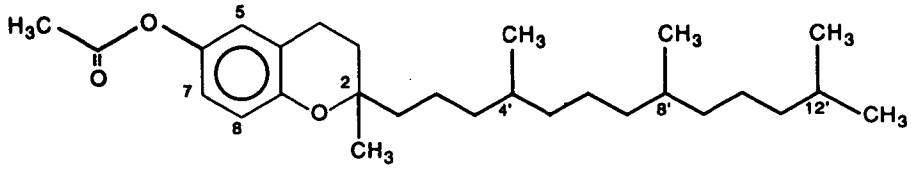
Position of methyls	Trivial Name	Trivial Name
5,7,8	α-tocopherol	α-tocotrienol
5,8	β-tocopherol	β-tocotrienol
7,8	γ-tocopherol	γ-tocotrienol
8	δ-tocopherol	δ-tocotrienol

B **RRR-α-tocopheryl succinate**



Common name: d-α-tocopherol succinate, Vitamin E Succinate
Trivial name: RRR-α-tocopheryl succinate
Chemical name: 2,5,7,8-tetramethyl-2-(4', 8', 12'-trimethyltridecyl)-6-chromanol succinate
Molecular weight: 530.8
Empirical formula: $C_{33}H_{54}O_5$

C **RRR-α-tocopheryl acetate**



Common name: d-α-tocopherol acetate, Vitamin E Acetate
Trivial name: RRR-α-tocopheryl acetate
Chemical name: 2,5,7,8-tetramethyl-2-(4', 8', 12'-trimethyltridecyl)-6-chromanol acetate
Molecular weight: 472.8
Empirical formula: $C_{31}H_{52}O_3$

Figure 1. A: structure and nomenclature for 8 naturally occurring vitamin E compounds. B: structure and nomenclature for RRR-α-tocopheryl succinate, succinic acid ester derivative of RRR-α-tocopherol. C: structure and nomenclature for RRR-α-tocopheryl acetate, acetate ester derivative of RRR-α-tocopherol. This general information is a compilation of information from References 1–4.

Quimica Nova 12(3) 1989; 297-298

THE PRESENCE OF GERANYLGERANIOL IN Bixa Orellana Linn.

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Recebido em 15/02/89

Abstract: The diterpene, geranylgeraniol, is present in the Bixa orellana's seeds, together with bixin and other carotenoid diacids which are responsable for the coloring action of these seeds. This diterpene is being reported for the first time in this genus and probably is reponsible for some unusual properties associated with the crude dye extracted from this plant.

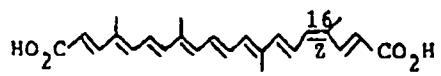
Introduction

Bixa orellana Linn is a well known and studied plant of the Bixaceae family which is widespread in all tropical America. Its seeds produce a natural dye used by the Amazon Indians to paint their bodies and is now also being used for coloring food, cosmetics and other products.

Bixin, the monomethyl ester of 4,8,13, 17, tetramethyleicosa-2,4,6,8,10,12,14,16,18 -nonenadioc acid (I), the major dye constituent of the Bixa orellana's seeds, occurs in the plant in the 16-cis form, and is easily transformed to the more stable trans form , known as isobixin (II). The free diacid is also present in the dye and is known as norbixin (III). (1)

BIXIN (I)

ISOBIXIN (II)



NOR-BIXIN (III)

The search for safe natural dyes, as a substitute for synthetic coloring products in the food ans cosmetic industries, has stimulated the development of several commercial coloring products based on this carotenoid mixture, directly extracted from Bixa orellana's seeds.

Its use as a histological dye was also recently porposed (2) and its specific property in being fixed, by lipophilic cells, prompted us to examine in more detail the chemical composition of the coloring material present in the external parts of the seeds.

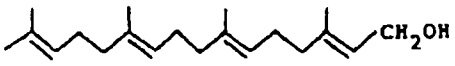
Result and Discussion

The ease of fixation by lipophilic cells of the dye mixture from Bixa orellana's seeds could not be explained easily in view of the relatively polar structure of the dicarboxilic acids, which are responsible for the coloring action. As a matter of fact the carboxylic acid salts are very soluble in water and can be used to give colorful red and yellow solutions to aqueous medium. It is also known that the dye has a "greasy" aspect when directly expressed from the seeds by hand, generating the special property, use by the Indians, which makes it suitable for body painting. This property makes the Bixin's dye very similar to lipstick, which is a combination of dyes and Cocoa butter.

These observations probably indicate the presence of another substance in the mixture which can work as a "vehicle" for the carotenoid acids and explain their unusual properties.

In fact, extraction of the external parts of the Bixa orellana's seeds, without allowing the extraction of the triglicerides present in the internal part, followed by partition of the dark red extract by silica gel chromatography, allowed the isolation of several colored fractions all related to the carotenoid diacids, and an oily fraction eluted in hexane:chloroform (8:2) and present in approximately 0,1% yielf of the total mixture. This oil was purified by preparative TLC, analised by 60 MHz PMR, IR and MS and

identified as geranylgeraniol (IV) a well known diterpene occuring in several species (3-5). The presence of this diterpene alcohol which as far as we know is being reported for the first time in this species is probably responsible for the unexpected properties shown by the mixture of diacids used as dye.



GERANYLGERANIOL (IV)

Experimental

Bixa orellana's seeds (500g) were extracted with toluene in a Sohxlett apparatus giving 17.1g of a crude extract. Silica gel chromatography using solventes of increasing polarity gave 55 fractions. Fraction 21 was dissolved in ethyl ether and extracted with NaOH 5% (5x30ml) giving organic and aqueous layers. The ether layer was washed with water (2x30ml), dried with anhydrous sodium sulphate giving, after solvent evaporation, 800mg of a viscous oil. This oil was chromatographed again on a preparative silica gel plate, eluted with chloroform:acetone (98:2) giving a pure material PMR (CDCl3) 60MHz: 5.30 (m, 1H), 5.05 (m,3H), 4.05 (d.2H), 2.0 (m,12H) , 1.65 (s,6H), 1.57 (s,9H). IR (film)(cm-1) : 3400, 2960, 2860, 1650, 1450, 1385, 1050. MS (m/z) (%): M+ 290(5), 275(8), 259(3), 257(5), 189(20), 177(18), 161(36), 159(14), 149(22) , 147(21), 137(48), 136(73), 135(47), 121(71) , 107(58), 93(84), 81(96), 69(100). Acetylation of this alcohol using pyridine/acetic anhydride gave a monoacetate which has spectral data identical to geranylgeraniol acetate (5).

Acknowledgements:

The authors are indebted to CNPq and FINEP for financial support.

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Polyacetylenes of Siphocampyla humilis (Lobeliaceae)

POLIACETILENOS DE SIPHOCAMPYLUS HUMILIS WIMM. (LOBELIACEAE)

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Recebido em 22/03/89

Abstract: POLYACETYLENES FROM SIPHOCAMPYLUS HUMILIS WIMM. (LOBELIACEAE).

Analysis of ethereal extracts from brazilian species of Siphocampylus humilis Wimm., gave the tetra-4E,12E-diene-8,10-diyne-1,6,7-triol, its aldehyde derivative, and the tetradeca-4E,8E,12E-triene-10-yne-1,6,7-triol, all previously isolated from others Siphocampylus and Lobelia species.

Recentemente registramos a ocorrência de poliacetilenos contendo 14 átomos de carbono, em 6 espécies de Lobelia e 4 espécies de Siphocampylus[1].

Estamos comunicando agora, o isolamento dos poliacetilenos 1 - 3, de Siphocampylus humilis Wimm. (Lobeliaceae), espécie posteriormente coletada nos arredores de Campos de Jordão (SP), em julho de 1987. A planta é nativa do Brasil[2], de pequeno porte (ca 20 cm) e rara ocorrência.

Estes 3 poliacetilenos foram previamente encontrados em espécies de Lobelia e Siphocampylus, sendo que 1 foi originalmente iso-